2028541504

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

24/11/92 Contacts / Consultants:- Confidentially

Areas: Allergy, Maternal smoking, Womens diseases.

Possible 'leads' - Rylander. - IAM to contact for possible contacts & Pains + Little?

Allergies + Asthma.

IAM - ask [illegible] re research on male hormones & ageing -
Women & epidemiology

Other issues - ETS and pregnancy.
[illegible] - RDC [illegible] and

ETS + children. Mental development - RIT
Physical development - Paediatrician / Epidemiologist

Garrod Most papers Med Sci Res December //
All Garrod's papers done - Warren - //

Ring John to confirm flights for Wednesday next week

(*John Garrod likes [illegible]*)

30/11/92.
Ring [illegible] / June Parry / Peter / Murray
Maternal smoking and ETS for McNas.
Ring McNas.
Read up on Garrod

2028541505

Articles of interest:-
Risk Analysis and Authoritative misinformation:

W C Harris "Today Chemist at work", Oct 1992
p22-27

Useful article about low dose extrapolation & current day [illegible].

N.B Magda Vogue Monthly report on October - "#C = Designer asking for [illegible] on [illegible]" - Membrane filtration.

30/11/92:-

Maternal Smoking and Maternal ETS exposure.

Following profs note from Marie Clare Nas asking about "Pregnancy and smoking, as well as pregnancy and ETS."

Probably the best basis for an immediate response is from Peter Lees Criticism of the most recent RCP report on smoking and children, the first chapter of which is entitled Passive smoking and the health of the fetus.

Major findings of report	PN Lees comments.
(1) Spontaneous abortions are increased in pregnant smokers by more than one quarter	Of the four paper reviewed in this book only one shows the supposed 27% higher abortion rate but this is a misquote as according to PN Lee no 0.27 RR is noted of several other references as this topic none account for all possible or even likely confounders and none claim causality. Also not all of published studies show an increase with smoking
(2) 'Premature labour is twice as common in pregnant smokers'	Apparently from review of '1982' 5 studies show premature labour more common in smokers but neither near 2X further 3 studies fail to show such relationship.
(3) "Babies born to mothers who smoke are lighter by an average 200g (approx ½ lb)" "and paternal smoking also makes babies significantly lighter."	Maternal smoking effect likely to be real - although quantitative estimate of 2 fold more likely considered exagg. Re paternal smoking Lee says evidence totally lacking. 12 studies show no effect, out of 14 supposed to show an effect only 2 remained after adjusting for maternal smoking.
(4) Stillbirths and early neonatal deaths (perinatal mortality) are increased by approximately one/3 in babies of smokers	There appears to be some evidence that this is true although the magnitude and causal relationship have not been confirmed and there is good reason to believe that smoking is not the only factor in these cases

2028541506

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

RCP report.	PN Lee response.
"The effect of smoking in pregnancy extend well beyond infancy with a reduction in growth and educational achievement."	To many confounding factors - unmeasurable - more likely to have an effect than smoking.
"An association has been reported between smoking in pregnancy and childhood cancers, although earlier studies found the association to be weak."	Citing evidence from 18 studies we conclude that the epidemiological evidence does not convincingly demonstrate this association
Passive smoking and effects in children -	Very often impossible to distinguish between maternal smoking effect during or after pregnancy.
Over 1/4 of the risk of death due to SIDS is attributable to maternal smoking	Of 10 studies looked at - all showed an association for first 11 weeks (more after) possibility of confounding not ruled out so many factors have been reported as linked to SIDS that have not been sundried in this.

Ring MCNas - #845

Keith Ware:-
Would like to have the scientific

Doesn't want to come together: Does want written response if possible - if not then this was only a personal request and not that important if doesn't want to waste a day having a meeting.

Jim Parry:- Not in until Friday

Wendy Burrell - not in until December 10th.

Talk to Her about Keith Ware - Business problems concerned CA not focusing on it - More than support the 'Science' - European regions may not be getting the service they deserve when with us in PMSA

HER Seminars:-

Possible Dates. Last Wednesday of each month - time 16:00h
= 40 min + apero

In English subject matter of your choice but should be understandable & of interest to all present.

Dates:- Feb 24. AKA = 'chaos'
March 31 CRN = "The product Development Process"
April 28 [HER?] "Burning Issues Question!"
May 26
June 30
Aug 25
Sep 29

2028541507

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

2/12/92.

Wang Yau et al. (1992). P.N.A.S. 89; 5804-5808. (Filed in Molec Biol.)

Parental bias of ki-ras oncogenes detected in lung tumours from Mouse hybrids.

C3H mice (low lung cancer incidence) crossed with A/J mice (high L.C. incidence). Reciprocal cross producing C3A & AC3 F1 hybrids. Spontaneous & VC & NNK induced lung tumours analysed for mutations in ki-RAS. The parental 'source' of the mutated gene identified, (Apparently A/J have slightly larger EcoRI site than C3H) and found that in virtually all cases the mutated gene came from the A/J parent.

This may suggest that the A/J gene is more 'susceptible' for some reason, to mutation - but don't know why!

John Gorrod -

Travel plans - Munich - sabbatical history of methemoglobin through aromatic amines - German influence historically!

CMC - still not - negotiating with college to use 'airheads'

Tsai w' Peter Crooks at Lexington since end September has synthesised nicotine glucuronide - now working on some other areas not sure what.

George Disselhorst still writing up - hoping to finish around March - has money until Jan. - Working all hours - still doing some experimental characterisation of metabolites of anabasine through rat & rabbit liver etc. found lung much much quicker - thought to be different form of FMO responsible but FMOs only just being characterised. Hoping to finish characterisation work looking at the effect of different inducers (Aroclor, PB, BNF & pyridine) Pyridine → Cyt 2E1 which has been reported to activate through work of Neil Castagnoli.

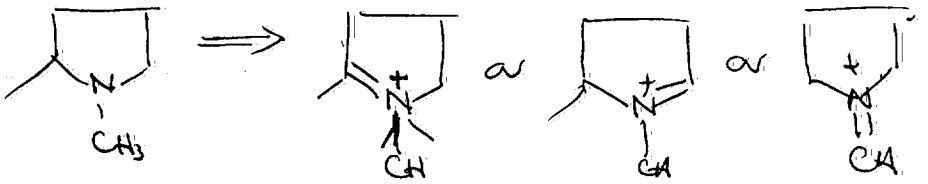
Sai - has synthesised & all objective minor alkaloids (approx 7) and has fully characterised (HPLC/GC/UV/IR/NMR/CMR) as four.

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

2028541508

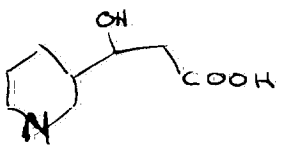
Yan Li - Cotinine metabolites - synthesised
Developing HPLC method for characterisation(?) then will compare metabolism diffs etc

Other Conrad interests — Particularly interesting - iminium ion.



Also similar to some other drugs (Haloperidine?) which shown to give Parkinsons like condition - Conrad interested to investigate the Pharmacologic activity of this further. - George Neumeyer published something - Conrad might be a bit pissed at this!) Adkafer showed interest but didn't follow through with any money At uni bit most someone involved with his application to Verbandt but no progress. May approach pharmaceutical industry or Parkinsons research group.

I asked him about Pharms interest in nicotine - basically v. little in Europe although more interest in states with Parkinsons disease & Alzheimers etc.

Interesting metabolite:-  ?

Schepers has also found it but Conrads group have found some startling characteristics which they think may have sig. effects on activity. Amazingly long ½ life for polar thought because it is so polar that it can't cross membranes - may even bind to proteins. Conrad going to talk to Schepers about it in Utrecht this weekend! (George Neumeyer published something on this surprisingly soon after a conversation with Conrad - suspicious?)

20285541509

Conrad also still trying to get money for nutritional countagens study which he mentioned before. If any money ever became available – he would like some!

ICG. Dec 3rd 1992

PM. In vivo assays targetting Multiple organs.

Collaborative sessions – Difficult compounds.

JNP. – Oral cancer P72 assay – 1 super researcher No ICRAS mut & no P32 adducts!! 80 year old.

Volatile compounds – paper – Peter Jenkinson.

"Methods for testing of Gases & Volatiles in Materials in Toxic Assays"

PDO. to be published in Mutagenesis.

cell cycle kinetics – Leigh Henderson.

Thursday 2nd June – [Cell cycle kinetics ?]

Microgel Single cell assay:-

for nitroso compounds tested – shape = pretty consistent

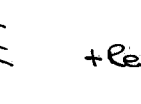
Comet assay applied on several tissues in human & rat & found v. useful & very comparable to alkaline elution.

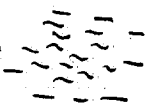
'Restriction site mutation Assay'. – J.M. Parry.

3 years ago – Did we dup a method to identify mutns in tissues of animals & humans.

PCR. technique

Basically measure mutation in Restriction endonuclease sites

+ Restr. dig. ⇒  ≈ 95% removal of wt.

amplify w PCR ⇒  ⇒ digest – completely removed.

RSM parameters – select target sequence – create RE site map. select primers.

To visualise product – use silver staining

Restriction digestion optimisation.

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

2028541510

Plasmids with oncogene inserts.
e.g. K-ras proto-oncogene cDNA inserted into plasmid
similarly for H-ras. - ie try to get RE comprehensive coverage of sites - RE ≥ 10% of genome - after optimisation probably around 2%
p53 in mouse } primer pairs - RE & effective cutting sites
α Haemoglobin in mouse } identified
Mouse ENU exposure - Tissue taken from DNA from Brain, heart, lung, liver spleen etc
Obviously could be a huge assay!. which tissues, which genes, which Restriction enzymes.
Xenopus laevis DNA α-globin
Tadpoles w NNNG & EP.
Can detect ≥ 10 mutants in 10⁹. ie 10^{-8}.
How to quantify.
Organisation of DNA dictates mutability!
Working on Transgenics.
Extending work to Oral tumours
Limitations to approach - Not alternative to transgenics
Transgenics prokaryotic - not eukaryotic
Peter Cariti.

John Ashby:- Transgenic Assay
to Cancer-case no problem.
Transgenics may be able to help in the non-genotoxics -
Write to Phil & Nigg with photocopy from book!
Prochloraz Mutamouse vitrotoxgene.
Write to Jim re possible invite?!
Env. & Mole Mut. last issue. - Debate on doses to use Mutagenesis or LD50 - too toxic for transgenics - debate to start in ENM - keep eye on this

Source: https://www.industrydocuments.ucsf.edu/docs/tcdc0000

2028541511

7/12/92

PEM - Request from Max Weetman - Any levels which have been increased rather than decreased historically? - please telephone back with details - possibly useful for an editorial - [Braxin -, ? - other?]

Christmas cards - "running" Norman, Keith, Jane, Chris, Martin & Steve

= Doug Spencer
Jim Barry.

Reply to Consi :-

8/12/92

Riding high on the TATA Box :- News & Views, Jack Greenblatt
Nature, 360; 16-17, 1992

3D structure of TATA Box binding protein (TBP) for Arabidopsis thaliana (= 40% conserved in all species so far!) TATA Box binding protein = TBP
TBP = DNA binding subunit of general factor TFIID required for transcriptional initiation by RNA polymerase II.

Last year discovered that TBP is required for transcription by all 3 nuclear polymerases
(Useful reference list for further reading)

From Infotopics: No 11. November 1992
p23: Swan, A.V. et al.
"Smoking Behaviour from Pre-Adolescence to Young Adulthood."
Avebury (1991) 231 pp.

p 25. Feachem, R.G.A. et al Eds.
"The Health of Adults in the Developing World." Ox. Univ. Press for the World Bank 1992 350 pp.

2028541512

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

p27. Mundell, J. "Direct tobacco advertising and its impact on Children." J. Smoking-Related Disorders. 1992, 3(3) 275-284

Ashford, J.R. "Problems in Assessing Smoking-related Mortality" J. Smoking-Related Disorders 1992 3(3) 263-274.

References:

Wertzman, M.D. et al. Pediatrics, 90(3): 342-349.
"Maternal Smoking and Behaviour Problems of Children".
(Filed for future reference - Abstract shows positive relationship!)

Phyllis Pine et al. Am. J. Pub. Health, 82(9) 1992. 1238-1243.

"Smoking Cessation in Women concerned about Weight"

Tried to investigate the possible role of weight control in the success or failure of cessation methods in women smokers by comparing cessation programmes with & without weight control programmes. Eventually found nothing!

2028541513

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

10/12/92.

S&T Newsletter goals.

Health, technical solutions

Putting things in perspective.

Goals: understand and investigate the effects of the product on Non-smokers.

"links/serve CA - build bridges

"Opinions/scientific response to articles in press etc - fire fighting

* Obtaining scientific information as soon & as comprehensive as poss

* links/serving Corporate Affairs - Responding to scientific Papers in 'press'. - w/legal clearance feedback of conferences.

1) CSA goals - see Draft. as recall.

2) S&T goals - ① + ② of CSA & build organizational goals

3) Strategy: ⓐ Regular meetings with CORA/ECC/Richmond/N.Y. - End of February ETS world conference - CSA staff meeting before EEC/CORA meeting after

ⓑ Develop "position and credible science" on all ETS issues

ⓒ Identify issues likely to be important in 1993 → 1994.

Budget status 1993 ⇒ $410,000 - must be app by U.S. for projects/grants/consultants

8. Defined areas

Issues.

- Membrane filters - 100,000 ② project.
  Asthma - André - lit rev of potentially ③/ $20,000 6 month - lit review positive response -
- Cognitive Dvp. - Schmidt-Kitsikis - RTP bias ③ - grant 40,000 12m
- Bayesian logic - waiting - hypothesis verification ③ 40,000 6-9 months
  Womens Bis - Marcham - SHB contract - lit review - CV etc 20,000 both lit review
- Reg. | Birth wt. - chip to project on big bucks } 1 month (P. poor) / (pan Phase) internal review
- (Physical dvp.) } ↓ hold - 3rd party lit Review. 'AM? } ETS & Pregnancy RDE.
  SIDS - "ghe contract Review 20,000 6 month lit review

2028541514

structured - paper having proposals for U.S.

Barker epidemiology

14/12/92.

References:-

G. Holmes et al & Davidio, 1992. Am. J. Med, 93(supplA): 30S-42S

Passive Smoking: The Medical and Economic Issues.

Review supporting E.P.A. -

Telephone call w Gill Barker.

Andrew - Budgets;

Peter

Helmuth

Mitch

Ruth.

Duncan.

Gill

Cary

Liaison - Med 40s epidemiologists publishing proj - SHS not possible eventual witness (contact through us) Canadian - favourable position ANTS - Meta-Analyses = New faces!

2028541515

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Video conference

S&T Strategy - 5 topics

Mayada - Metaanalysis conference

Mqpry - Market study for desk-top stuff -

Technical project - Action : ~~Market~~ Product Research in Membrane Filtration -

Patent literature}

Find out current commercial status and interest in small scale membrane filtration

End of January - Sutter, ... ~~...~~ *ANB *

Monthly meetings: ~~...~~ Friday 29th - morning January 9.00 - 12.00

Then last Friday in each month

Physical Development in Childhood - 2 months ... of ...

Pregnancy :- 2-4 months lit research

+ SIDS

+ Asthma

Contact SIDS - association in England - what they do + what they know

---

Identify areas of ... for secretary: ... - literature
Department budgets

ANB filtering of documents -

Prepare objectives -

Action ...

1. ~~Monthly report~~
2. ~~...~~
3. ~~...~~
4. ~~... Projects for US ...~~
5. Pary ...
6. ~~...~~

2028541516

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

1,3- Butadiene used as a target "carcinogen".

Claim that more 1,3-Butadiene from cigarettes than you ever get outside

Nayada to send copy of documents to Helmut:

Each group prepare alternative portion from comparison of building system - critique

BREEM. - Environmental UK. group - standards

+

Conference in feb 23rd Dinner - Tues. - Staff Meeting on Tuesday.
Wed + Thurs all day with closing Dinner.

Scenario for 'war Games' for February Meeting

HBI Athens presentation - Critical review -

Pre-conference (telephone conversation!) ~~11/12th Jan~~ Friday 22nd Jan.
Input for conference by 15th Jan!! - written or prgs. Telephone conference -

Reynolds additional contribution - tbc.

CIAR = Further money from outside groups - in London - (including Imperial, BAT, Bourneville, Japan Tab etc etc)

2028541517

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

JANUARY 1993

12/1/93

① EPA & ETS: -

Anne Okaniewska - Advocacy Alert.

"SIDS = "the mysterious illness that is the most frequent cause of deaths among infants aged 1 month to 1 year...."

For Wednesday

① See. library - can trace latest copy of documentation on carcinogens (NACR?-)

1/t - a 5th February for urbito hair discussions.

13/1/93.

Glantz & Parmley study.

N2. ♂ Rabbits. 0.3% cholesterol diet

					% Atheroclerosis	
16 High	= ~~NO~~ 1040 µg/M³, ~~CO~~	80.2 ppm.	tpm 32.5 mg/M³	82±21	45±12.
16 Low	30 µg/M³	18.8 ppm	4.0 mg/M³	36±14	21±23
32 control.	<1 µg/M³	3.0 ppm	0.13 mg/M³	30±19	22±15
				aorta	pulm artery

Results:- Weight gain - no group differences.

Alterations in lipids - No group differences. Total serum and triglycerides or HDL-cholesterol

Morphological studies:- Rgs: Aortic & pulmonary artery surface area caused by lipid toxicity

Correlation bet % of lipid toxicity & CO levels

Platelet function:- Table 3. two ETS groups showed bleeding time increased

Platelet aggregation ratio maybe due to ETS-11 Control = No dose response

2028541518

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

NB ① This article does not find any ETS-exposure associated increase in serum cholesterol or any other serum lipids.

In discussion say that atherosclerotic lesions in both aorta and the right coronary artery were positively associated to serum HDL cholesterol.

Too many non-sequiturs.

eg. "It is important to note, however, that we observed much larger effects of ETS than would be expected from a simple dose-based extrapolation from high doses experienced by smokers to the lower doses experienced by nonsmokers. Our results suggest that nonsmokers may be more sensitive to the toxins in ETS than smokers are, perhaps because smokers have somehow adapted to the chronic poisoning associated with active smoking. It is also probable that some of the biochemical systems involved are very sensitive to ETS, but saturate at low doses".

I would think that it is also possible that the model used cannot be directly extrapolated to the human system (high cholesterol fed rabbits?!)

2028541519

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

14/1/93 ISREC/UICC conference.

Philip Hanawalt, (Stanford, U.S.A)
"Role of chromatin structure and transcription in gene specific repair"
Protooncogenes susceptibility to mutation because actively expressed ∴ vulnerable or because not expressed & ∴ no preferential repair.
Need to know what genomic regions are subject to which conditions.

Jan Hoeijmakers, [Erasmus University, Rotterdam, NL]
"Molecular Analysis of genes involved in Mammalian DNA repair".

Excision repair (as dem above) slow in non expressed fast when gene expressed - preferential repair
eg. XP generally - X repair lacking of both types but one group (C) only lacking preferential.
Cockayne similar to XP-C

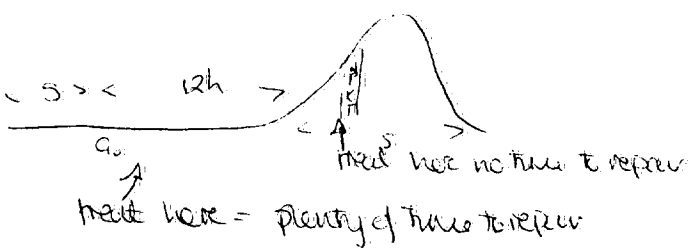
Yeast Eukaryotic RAD3

Syndrome - Brittle hair. PIBIDS- but no cancer proneness
Caused by NER defect involving > 3 NER genes

Veronica Maher, Michigan State University U.S.A
Carcinogen induced mutagenesis & variation in human fibroblasts - "Role of Repair"

HPRT gene - repair effects on mutations ① compare repair deficient
XP12BE - devoid of Nucleotide Excision Rep (NER)
② Also synchronised & time controlled - for allowing diff repair times.
③ Retreat w repair inhibitors.

Time - S phase early stage = HPRT experiment



≏75% G1 where mutated are in NT strand - but in G1 phase 100% in Non transcribed
XP cells confirm this - 75% of G1 a S = Non Transcribed

2028541520

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Domains of repair – Transcribed - 1st
Nontranscribed - 2nd
Non expressed - 3rd.

Nitropyrene – C8 Guanine adducts
= Inhibitor wait;
But Methyltransferase is not strand specific
Alkylating agents – Methyltransferase will repair.

Peter Cerutti

"Genotypic mutations in cancer-related genes".

From P Hainaut pres – ?
What are rel. genetic regions?
What type of genetic change → activ.?
What agents?
Is the region silent or active in target tissues?
RFLP/PCR approach – genotypic as opposed to phenotypic basis
① Remove wt.
Mutant standard added after removal of wt

H-RAS – in human. – Urinary bladder 46-16%
Oral 39%
Thyroid 26%

2/3 = codon 12. 85% – G → T. (CGC → CTC) – could indicate carcinogen specificity
CpG dinucleotide – hypermutable site? (what is a CpG dinuc)

Smokers – detect in bladder tissue pre-tumoral HaRas mutns?
– Results not yet.

p53 organ & tumor specificity in mutations maybe due to rep context
Exons 5-8 mutns – Hotspot codons 175, 248, 249 etc etc
(= outside functional (y identified)
Hotspots must be at DNA level because all mutant protein are OK
CGG = dinucleotide CpG dinucleotide
248 hot spot in RE site
Hepatitis
Aflatoxin B1 seems to produce same mutn (249 AGG → AGT) most frequ (17)

2028541521

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

found in high incidence regions (see CC Harris work)

Richard Albertini (University of Vermont, USA)

"Somatic Mutations in human: quantitation & molecular characterization"

Biomarkers - environmental monitoring
Reporter systems HPRT in T lymphocytes - (NB smokers unusual ↑!)
Sensitivity & Specificity

Perera article - foundry workers Helsinki (1992 Cancer Res)
PAH-DNA adducts = best exposure ind.

Breast cancer patients treatment w multi freq - chemotherapy
with alkylating agents assoc w v. high freq.

V(D)J ACTIVITY

CC Harris (US Nat Cancer Inst; Bethesda)

"Mutations in Cancer related genes in human tumours"

Aflatoxin story w P53

Do p53 mutants vary in their pathological effects in same cell type
Do pathol effects of specific mutants vary in cell types
In vivo models using

p53 mutational spectrum - differs among diff sites - lung tumours - some evidence of differences in ethnic groups.
Mutational hotspots - CpG sites (C→T at CpG sites)

Early a late event?

p53 mutns - not equally rate limiting in all tissue types

Bondiogenic neoplasia - relatively early event - also in esoph, breast, skin etc
but late in colon, bladder and brain
p53 mutn (a protein accumulator) indicator of poor prognosis

Transition at CpG - sites (i.e. RNT) predom in colon cancer etc.
but i.e. RTR tran versions most freq in lung breast exptl tissue
is associated with bulky carcinogens
A Non-hallmarking strand bias in lung and breast cancer

2028541522

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Association

AP b, + cod 245 ser
Sunlight and? ...
e.g. smoke + G-T transversion

Frank Rauscher III (Wistar Inst, Philadelphia, USA)
"Tumour suppression & transcriptional regulation: studies on the WT1 Wilms tum gene"

Wilms Tumor
Kidney early onset heritable form.
Most frequent solid tumour in children Her. - 5%, Sporadic 95%

Other disease syndromes - WAGR
Beckwith Wiedemann Syndrome (BWS)
Denys Drash System

- The H 11p13 WT1 gene - 4 zinc fingers of C2-H2 class
Normal expression in kidney (spleen) + blastemal cells
Also Testes, Ovaries, Brain } in adults.
compared to other tumour suppressor genes
Role in development
Zinc finger = DNA binding
Wilms tumour needs to bind DNA but also needs other function like repression
What kind of target genes are regulated by WT1 ?
Should be overexpressed in WT etc
IGF-II

CARCINOGEN INDUCED CHANGES IN GENE EXPRESSION

Tom Curran, (Roche Inst of Mol. Biol., U.S.A)
"Fos + Jun: inducible, oncogenic transcription factors".

Cellular immediate-early genes -
Cysteine residue in middle of DNA binding zone
Oxygen regulation but not disulphide bond

2028541523

Truncated fos with cysteine → serine change ⇒ more transformation
Cysteine presumed oxidised ∴ don't know if Age modified.
-Now identify cellular modifier

Ref 1 bifunctional protein with both redox & DNA repair activity.
Redox activity - cysteine residue in fos & jun.
Redox regulation may function as a general mech. for controlling transcription factor activity.

Transgenic mice experiments:- c-fos/lac2 fusion gene

fos v. highly expressed in stratum corneum & hair follicles
N.B. not assoc w proliferation sites - more assoc w terminal differentiation
fos associated with cell death? - carcinogenesis plates hyper - keratinocytes

Palate Resorption high expression = cell death? or differentiation

Peter Herrlich (Kernforschungszentrum Karlsruhe, FRG)
"Carcinogen-induced regulation of immediate early genes"

UV response
What is the primary event - is it DNA damage? Yes -
UV stimulates the transactivating function of jun

UV induces phosphorylation & dephosphorylation of jun

DNA lesion - recog by protein - unknown signal generation ?transduction regulation of transcription.

but - lost of talk destroys then pretty picture!

MAP 2 kinase

2028541524

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Robert Eisenman. Myc/Max (Fred Hutchinson Cancer Res. Center Seattle USA)

~~Requirement of ptn kinases in cytoplasmic~~ signal transduction

"Myc functions as a nucleoprotein complex"

Myc turned 'on' with mitogen, off w differentiation.

Myc synthesis maintained throughout cell cycle.

Transcriptional activating domain?

'C' terminal - 100 a.a. homology to transcription factors

helix-loop-helix + leucine zipper (i.e. protein-protein int)

∴ contact DNA for binding.

∴ ought to be a transcription factor?

But no homodimerization or heterodimers of other known

Identified Max - new protein w which myc form heterodimer.

(p22Max & p21max)

In vitro - Max preferentially heterodimerise with all myc.

(will also homodimer)

- also complexes have DNA binding activity

in vivo - also found max protein pres in all cells

found myc mostly associated with max - but max stable

but myc v. short half life

Max doesn't appear to be regulated at <u>all</u>

[CACGTG] binding

∴ it is Myc that regulates not Max.

<u>Max</u> homodimers may repress transcription - possibly passively

but when myc is induced ⇒ activating complex & displaces

the blocking <u>Max</u> homodimers

- Then looked for more Max compliments and found

another found Mad (- again like myc + max has HLH-zipper region)

Only protein that Mad interacts with appears to be Max.

Mad-Max - also bind CACGTG region

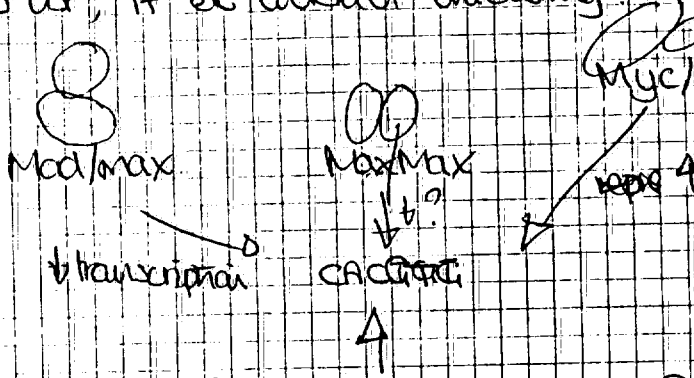
Mad↑ when myc ↓ during differentiation

Max at centre Max+Myc = +ve regulators

Mad Max = -ve regulators (MXI, similar to MAD; Ballinger lab, [illegible])

2028541525

How UF, TF etc interact interesting



Mad/myc - feedback loop? - very important question - not answered yet

Eilon Nigg (ISREC)
"Cell cycle Regulators."

cdc mutants in yeast (S. pombe)
cdc2 kinase = protein kinase

cdk = cyclin dependent kinases

How are these regulated & what are their targets

Dephosphorylation of cyclin residues in late anaphase for entry to mitosis

Cyclins as oncogenes? - cyclin D1

Destruction of cyclin

Dereg cyclin may be oncogenes
Cyclin B destruction required for cells to exit from mitosis
cyclins have specific cellular distribution

N-myc knock out mice → lack of branching of many epithelial organs including lung

TGFβ inhibits branching
" suppresses N-myc expression in epithelium of lung bud organ culture

2028541526

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Harold Moses (Vanderbilt University, Nashville, USA)

"Role of nuclear factors in cell cycle regulation"

TGFβ superfamily

TUMORIGENESIS LESSONS FROM HUMAN TUMORS & ANIMAL MODELS

Ellen Solomon (Imperial Cancer Research Fund Lab., London)

"The Molecular basis of acute promyelocytic leukemia"

build up of malignant promyelocytes cannot progress to granulocyte

specific translocation = t(15;17)(q22;q11-12) (always & only)

Breakpoint identified of Retinoic acid receptor.

Ubiquitous expression, multiple transcripts (PML transcripts)

Ring finger family

Cysteine rich regions almost entirely conserved

PML - RARA + ISL

5' or 3' breakpoint? - no correlation w clinical details

Anton Berns (Netherlands Cancer Center, Amsterdam)

"Transgenic mouse models for cancer: identification of synergizing oncogenes"

Eμmyc transgenic mice

Myc Pim mice - destroys before birth: PIM/Myc collaboration

also Pim bcl-2 etc:-

What are "knock-out" mice

Chymeric systems w mice & ES- ~~deprov~~ lots of ?'s

2028541527

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Monday 18/1/93

① Call ~~with Reiningens~~ - See HSE/IAM re plans'.

② Refreshments for 24th February.

③ Write up ISREC

④ ~~See Gill re Yellow sheets~~

⑤ ~~[illegible] force [illegible]~~

⑥ ~~Hairdresser~~

⑦ ~~"Li Tracy" / Drawer'~~

⑧ Spanish.

⑨ MAP - Goals/preparation

⑩ Check if Schoendorf article ordered. J Am. Ac. Pediatrics. December.

⑪ Prepare for Oxford conference - see programme. New Projects?

⑫ Book flight → Oxford

From Indoor Pollution News:- Dr Kenneth Schoendorf:- SIDS. xx [illegible]

⑬ Jill / Cory - SHB lists'

⑭ Ask Rosemary for searches on Casarett's Toxicology'

⑮ 1,3 Butadiene studies.

2028541528

Thank you for organising such an excellent meeting last week and for allowing me the opportunity to try and understand the progresses being made in genetic research in cancer force. I completed my PhD (in genetic toxicology) and moved into an industry "desk" job. I have always been determined not to lose touch with the real science. Unfortunately this is not always easy to do, even attending conferences and reading ~~pub~~ reputable journals is often not enough. The quality of the speakers and the clarity of their talks has helped to clear up many questions that I had been confusing me in the literature lately with such an excellent format was available more regularly, and at such a convenient location.

My congratulations to you and your colleagues in the organisation of such an excellent conference. You should be very proud of the progress that you and the other speakers are making in this field.

2028541529

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

19/1/93. Conference call. 22/1/93

Projects: 5 projects for S&T in 1993

Progress to step II

① Appropriateness of women as surrogates for

ETS & Pregnancy. -

② Why? - Children RCP - 1992 Children

SG - 1993 Children

EPA

③ ETS & Physical development of children.

- check database on children & making - paediatrician or specialists

④ ~~ETS~~ & Cognitive development & Parental smoking

RDE - Wed/Thurs ETS - meeting N.Y. (24/25/26)

& Witorfe

—— // ——

EPA impact in Europe - Any other examples of Class A carcinogens acc to US: which are not accepted in Europe.

NCI list compared to European list

precedent for Europe

- target → Carcinogen information.

* Feb meeting how does ~~Europe~~ react to EPA *

See Previous

'Official' lists of classified carcinogens throughout the world.

NCP - Annual list of carcinogens? -

Toxicology book.

([illegible] 'social [illegible]' project for HCC (from RIT - Task force PEM/RIT/IAN/ALA/UC)

Matt [illegible]

Dav[illegible] [illegible] - EEC - EEML

Social [illegible] [illegible] at NIT - at what level - formal/informal

RIT - put together Social [illegible] project as discussed with UC for HCC

2028541530

27/1/93

Res - 5681 - Science 11 Dec 1992

EPA - Report on ~~ETS~~ EMF due to come out in 1993. (hold on)

Women + Smoking

Introduction p 8 + 9 actions proposed strategy!!

p17 - Maggie Thatcher worked with PM "to help open up Markets in the Third World".

p26. How are Women exploited by the Tobacco Industry

p32 Countering the pressures to use Tobacco.

p34. Preventing Tobacco use in Children.

Repeated emphasis on smoking as an image / friend counselling.

p53 "Big threats"

Thursday 2pm

a.m. - ISRCC Meeting
- In Brfo preparation
- See Rosemary re cancer lists + other

2028541531

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

28/1/93

Toxicology

Find out current position on toxicology / regulatory status & pending status on use flavouring with a view to identifying alternatives?

① Talc - as a tipping release - possible alternative titanium dioxide

② Cooked flavours - Maillard reaction - (pyrolysed amino acids?)

③ Denaturants for alcohol - Methylene blue - current
FDA #4 not legal in Germany.

---

① Talc as a tipping release:-

General - 1970s/80s reports of industrial exposure to talc linked to cancer in e.g. cotton industry etc

Some animal studies showing talc as a mediator in B[a]P studies & for other chemicals

NTP - Baby powder inhalation => adult resp distress syndrome

March 1993 - Health Assessment Document on Talc CPA
"Limited data suggest that talc is not carcinogenic following inhalation exposure ....."
INADQ = Inadequate data

Talc used on belts to prevent sticking.

2028541532

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Jessica Tullin - 1st

~~DNA Repair~~

Session on DNA repair & DNA damage

7:30 – 5:30 = 10hrs/day 5 days/week

= 50 hrs/wk.

~~10hr/hr ≈ 500hr/week = 2000hr/month~~

Total days worked :- 52 x 5 - 6 x 5 / 12 (per month

= 46 x 5 / 12 = ~~230~~ / month

∴ ≈ 220/ = 19.2 days/month

∴ 19.2 x 5 x 10 = 1,920 hr/month.

∴ 2000/m = 10.42 hr/hr ≈ 4% rise !!

2028541533

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

29/1/93 4 TAC * SHB

Cancer disease – what [illegible] genetic predisposition – follow up!

WM – [illegible] release [illegible] from ASPC..

* Shona.- Ring Loreen McAlpine re [illegible]

SHB folders:-

Bob – [illegible] response [illegible] from [illegible] –

Just [illegible] conference [illegible] CPA [illegible]?

"News [illegible]" European [illegible] – proposed [illegible] analysis

Sweden / Switzerland

TAC [illegible] come back from [illegible]

HB study = STACK?

[illegible] Bus [illegible]?

Social! –

Children [illegible] ⇒ [illegible]

Women [illegible] – not discussed with RPA

Integrated workplace study – policy ——

Women? – low priority – [illegible]

e.g. "bad" environment

Ev. Project files: Papers etc.

Consultants – recruitment –

La [illegible] de fonds. March 13th Le Petit Paris

Loreen.. [illegible] 252 + 2090 +

Sunanda Wienda:-

Children Washington [illegible] October

by 100 days of [illegible] report – Youth & [illegible]

Joe do Franca – Jo Cowell [illegible] contributing

2028541534

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In Byfo - ?s for --

Richard: Talc / Maillard reactions / Derivatives in talc
? any interest / input in projects / consultants program

2028541535

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

02/02/93

INBIFO

CR 2978 ⇒ α HCA pyrol. prod of CR2978

↓ Acrolein ↓ w CR2978

CSG Nicotine data:-

Increase metabolites with the addition - stat sig - but same trend in all three time points

'ask for creatinine?

⇒ Liver enzyme induction -

Nicotine metabolism - induction in rats? / humans /

Tewes

What are major factors of cigarette design which alter Ames activity

Burley, filter efficiency, filter ventilation, paper porosity } / mg basis

citrate / phosphate

30 cigarettes in other assays:

Spargate "tobacco soul"

WIDE ↑ mutagenicity ~~mut~~ w ↑ ∅ - ↓ burning Temperature — Rep. from Ted: length, puff no., TPM/Vol ratio

Filtration more likely than burning temperature.

Filtration with puff velocity ~~very~~ documented.

Cytotoxicity. 2R1 control

Mouse 3T3 cells.

Conclude not biologically relevant. - Assay not sensitive enough?

Rel. test slope and EC50 No

Stat sig but not biologically *relevant?

Not stat significant when compared to intrinsic variation within cigarette

* Richard NY - end feb? *

~~Filler density~~ filler density studies?

2028541536

Diesel/ETS/ studies.

Relative Diesel exhaust exposure? – 10µg/l. = sort of particle control.

RASS - Room-aged sidestream smoke

SD laryngitis? – too short?

[Rat lymphocyte studies?]

DNA adducts. ~~8~~ 8-OHdG. - Mass spect.

⇒ RFLP analysis of codon 12? p53 transversion mutation?

DNA strand breaks – Bronchoalveolar lavage - problems with this?

8-Hydroxy-deoxy-guanine

Hb adducts?

Bladder / Blood

Lipid peroxidation: carcinogenesis!

Surely should look for more ST endpoints already well documented for MS

Evidence of "uptake" e.g. Hb adducts:-

To measure if "exposure" is working.

Generation of Diesel exhaust.

Clearance

Laryngeal intubation (canine)

Hb studies - adducts PAH?

[32P adducts?]

Testing/worst burning stove/

1,000 (10⁶)

2028541537

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

03/02/93

Cerny Nixon - Heme-Oxygenase

HO = p32, SH30 oxidant stress protein

Induction - Haem a sulphydryl(?)

GSH unvariant - depletion or conjugation TPA v Sodium Arsenite

2 possible induction pattern for TPA: - SH (cysteine prototype)
Phosphorylation (PKC)?

DMSO as inducer

Cycloheximide translation block.

Is ongoing protein synthesis required?

Arsenite is sensitive - Concurrent.

CHX induces alone at appropriate doses more so than TPA

Pretreatment: - No effect of CHX - cells recover?

Protein synthesis reduction required for super induction

Transformed cells different.

Jos ~~induction~~ inhibition

Inducing agent either sulphydryl reactive agents
Sulphet oxygen(?)
Heavy metal ions cd++(?)

Other active oxygen, non independent systems NO?

2028541538

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Over expression of catalase - introduce into mice lungs e.g. virus aerosol particles?
Expression stable after 10 passages - dependent on culture conditions
Any phenotypic changes? - No
Diff sensitivity to smoke whether confluent or subconfluent
Number of targets?
independent of
Alkaline elution far away from confluency - fixed cell number.
Phosphorylation pathway - antisense ⇒ under expression of ~~the~~ fos.
K.O. mice?
K.O. AP1 site of protein of haemoxygenase?
~~As~~ fos system followed to an endpoint?
Idea behind catalase cell line to learn what happens in a cell where there is no base DNA damage.
Hazleton studies with transgenic mouse ⇒ no mutations in smoke exposed animals - inappropriate system?

Karyotype analysis of transformation? Regular - transformation assays with thermosensitive mutants? - Probably not
Avian transformation systems.
Transformation system cannot ~~also~~ descriminate cigarettes but can give yes and no answers.
Could use to show significance of fos mechanisms?

*Current Annual practical act:- * to Roger

Sensory physiology assay

Anatoxin more potent than nicotine

Keywords for AC - fos, transcription
Cystine

2028541539
Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Nicotine studies:-

urine 94% faces 3% body <1%

metabolite profile of nicotine in rat.

Comparison of S-nicotine with R-nicotine:-

Differences.

independant of induction status or sex there is a higher excretion of nor nicotine in S or R.

Also some of differences which are dependent on induction

Diffs for cotinine, N-oxide etc etc ~~Less~~ Differences as in both directions

Differences in sex for B in S but not in R.

Also K = 7% in ♂, acute induced rat with S nicotine only

Summary:- Almost all metabolisms for S also found for R with the exception of K.

sex related differences are more expressed for S nicotine than for R-nicotine.

NN'O - S nicotine = cis NN'O - R-nicotine = trans

but 3 HOC S & R predominantly trans

Could use to descriminate level of induction - could this be useful in CR studies? - used but showed no state of induction tiny dose changes - may be crucial to ~~interpret~~ ~~in~~ interpretation of CR lines - CISC - with racemic nicotine did not find any dose effect -

Any information from chronic or acute - to some extent will be answered from Nicotine now.

Sex differences in humans as well? - Relevance re women study - use of women as surrogates

Deuterium nicotine from other sources - published 1991

2028541540

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Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Nicotine Accumulation in Hair

NI induction of rats reduces nicotine uptake in hair!

Human ETS exposure - increase with time -
Black hair accumulates more than other
age of hair very strong effect of uptake in hair -
also some indication of saturation
at start of experiment - virtually zero!!
After washing repetitively reduces to about 60%

KE publish to show that hair concentrations do not represent exposure
One publication
what are the objectives of this study should proceed

Nicotine patches - N-nitrosamines.

why?

2028541541

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Rabbit Atherosclerosis study

Rabbits - New Zealand male rabbits

Diet :- Cholesterol 3% Soybean oil
+ control diet

Exposure groups:- ETS-High = 4 cigs/8 mins

Time of exposure :- 2 wks → 12 wks

① 4 cigs every 15 mins } ETS-H
6 hrs/day 5 days/wk

② " MS- 20 s @ through 10 mm ϕ tube } ETS-L
15 mins, 6 hrs/day 5 days/wk

③ same exposure chamber ○ exposure

④ CO only exposed group *

? ⑤ CO dose comparable to early group *

? ⑥ add dietary control group *

- Exposure measurements :- Nic, TPM, CO other?

CHb

~~Serum cholesterol~~

- Endpoints :-

*= addition/improvement to Sci-Exper

2028541542

?

?

No total

Normal diet may be stress control.

No/group
Details of exp
Dose/resp

Should use standard equation to obtain same yield rather than same wt.

2 CO doses?
adjust mac?
?

?

Any other components which might be readily available elsewhere worthy of measurement

Methods for measuring TPM?

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

04/02/92.

⇒ Room aged sidestream smoke - How does this effect the quantitative qualitative comparison to MS smoke?
N.B Nicotine & NH_3 reduced with ageing and materials (and formaldehyde)

But Acrolein and Aldehyde do not seem to change - stable in both fresh and Room aged sidestream

90 day histopathological changes - after 90 days - hyperplastic at up doses of 2 & 6 µg/ml TPM - What significance does this have with respect to a longer term exposure.

What in the smoke could be causing these changes and how Could you predict that the room aged smoke would change this.

How sure would 'reversal' be?

Low ignition propensity cigarette - biological testing

Initial ignition test should be out by August - but unlikely.

legislation on smoking and health issues which will involve regulatory assessment of non tobacco ingredients - to office of smoking & H

: publication of methods - no reference to ignition propensity

use ETS request for publication

What about a series of publications on the overall concept of standardised, meaningful product testing?

2028541543

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Signal transduction: Health & ageing

*Signal transduction - fos/jun/AP-1 sites etc *.
linked to cellular homeostasis.

Hormones - TSH direct nuclear reaction
TIBS - October 1992 - Signal transduction

09/03/93

Nicotine in hair -.? - Review Objectives

Thrust to get out confounding factors:-

Indications that chemical treatment is influencing the nicotine levels in hair -

Why some facts in Rat hair follicles accumulate nicotine which rest without growth for several weeks by

Melanin probably plays a role in uptake/binding for nicotine

Cotinine around 10% of nicotine - steady state serum-cotinine should be around 20% but ~~need~~ need to check steady state serum (being done by CSE) - for brown norway

SD = different

S v R nicotine not sufficient evidence for a difference between R & S binding

Could analyse data on a total basis as well as on a per wt of hair

SD not that much different from untreated ; not impossible that the source of this 'hair nicotine' may be the same for both (ie external contamination - slight increase over untreated could be through grooming/saliva contamination

External uptake - little influence of pigmentation

Possible indication of the ageing of hair - 40cm distal part

Could look at the same hair

Higher concentration of nicotine means its not deposition that is being washed out - or at least not entirely

2028541544

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Difference in ETS exposed v smokers hair in washing.

Seems that systemic uptake is not washed out
∴ ponbry could predict smoking vs ETS uptake?

Data extrapolated from experimental exposures to estimate or model the effects of systemic v external uptake

Calculation of systemic exposure

Aim - Are we interested in quantifying systemic uptake.
- probably not - probably should concentrate on the factors in hair which effect this :-

- Bleaching
- Pigmentation
- Ageing of hair
- Ageing of person

Source: https://www.industrydocuments.ucsf.edu/docs/tsc10000

2028541545

Tuesday 16th February 00 44 272 636626

1. ~~Hilton Club de Vacances~~
2. In Tray
3. Expenses
4. ~~Ring Bob / [illegible] re Hotels & flight to N.Y. from Richmond~~
5. ~~Sort out Briefcase~~
6. ~~Protocol for [illegible] & [illegible] to [illegible]/Richmond etc...~~
7. Ring Richard re Richmond trip on Monday
8. Ring Robin & [illegible] re Richmond trip - 2 nights?

Thursday Feb 18th

1. ~~Finish protocol~~ fax to Rob, WRC, [illegible] etc (Ring Bob = copy?)
2. ~~[illegible]~~
3. Ring Bob - protocol?; visit Monday.
4. "In Tray"
5. ~~Sort Briefcase~~
6. ~~Write to [illegible] Association~~
7. ~~Green book - fill in February~~
8. Prepare for 'States' visit.
9. ~~Ring [illegible] Act. [illegible]~~
10. [illegible] re nicotine in cloth
11. Ring WRC re protocol.

2028541546

Current contents: -

p20 Multimedia.
p41 - Brochures & Biography.
p70 Mid Brief & Gen
p88 Microbiol & cell Biol
p101 Physiology
p136 Physical
p151 Exp Sci & Med.
p173 Clin Med.

~~p31-32~~ ~~p51-71~~ ; ~~p74-7~~ ; ~~p112-119~~, p124
p126. 1171, 1176, p124
p137 1284

p146 - 1, 12
p152, - Journal
p154
p207

Some library journals: - Scientific American · 26(6) Dec 1912. p 89 92.

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

2028541547

CSA Staff meeting - 23rd February

* Briggs - Robens * Guildford Survey

John Graham Harvard Risk analysis - Policy making using meta analysis -
3rd party organisation

Lead legal Workplace

Brussels meeting.
(IARC - symposium)

2028541548

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Sunday March 7th. 1993:

From:- Br. J. Ind. Med. 1992; 49: 601-605. M. Tubiana. French N.I.A.S.
Editorial entitled "The carcinogenic effect of exposure to low doses of carcinogens".

"In a recent editorial Abelson, associate editor of the journal Science, wrote that "stringent regulation and frightening publicity have led to public anxiety and chemophobia.... the cost of cleaning up phantom hazards will be in the hundreds of billions of dollars with minimum benefit to human health. In the meantime real hazards are not receiving adequate attention".

"It can even be argued that too stringent regulation can be detrimental - for example, the ban on potent insecticides such as DDT has resulted in an increase in the incidence of Malaria in India and South east Asia. It has been asserted that banning DDT without replacing it with inexpensive substitutes may have caused several tens of thousands of lethal cases of malaria. With regard to CFCs, their possible impact on the ozone layer in the polar regions has to be balanced against the benefits of an inexpensive technique of food refrigeration, which has been one of the most important factors in health improvement during the 20th century. We must remain vigilant and should not accept that an increase in the cost of refrigerators jeopardise their use in developing countries. Similarly the overestimation of the detrimental effects of radioactivity has hampered the development of nuclear energy and favored the use of coal and fuel, the combustion of which produces carcinogens and induces a greenhouse effect; thus fossil fuels may have detrimental effects on health far greater than those of nuclear energy. These examples show that overestimating the risks of of a chemical or physical agent has consequences that ought to be taken into account. The realistic assessment of the carcinogenic effect of exposure to low doses is therefore of great practical, financial, and scientific importance."

N.B also "The incidence of lung cancer in non-smokers has remained constant (Source NIH) despite air pollution" If this quote is correct then ETS is not

Source: https://www.industrydocuments.ucsf.edu/docs/fcdl0000

2028541549

WE 12/13

carcinogenic"!.

Refs to follow up on:- ref 12. "Muir, C.S. Epidemiology, basic science and the prevention of cancer. Implications for the future." Cancer Res. 1990; ~~[illegible]~~. 50: 6441-8.
(cited with reference to dose relationship calculation for tobacco & cancer
$F = a d^2 t^4$ — fitting chiefly at the higher dose levels).

Monday March 5th

from Rep. -
① Find out about IARC Directory of [illegible] Research - [illegible]
Dusseldorf

Roger Walk - [illegible] information re [illegible] study

University of Dusseldorf - [illegible] & Germany meeting -

Prof ~~[illegible]~~ Schinder Head of Pharmacol. [illegible]
much experience in [illegible] - [illegible] prepared to run
studies for industry & as consultants ([illegible])
2 possibilities - [illegible]
- or [illegible] with consultant [illegible]

Roger Walk / [illegible] [illegible] experience [illegible] 83/84
[illegible] 84/4 [illegible]
[illegible] group [illegible]
[illegible] by industry [illegible]
the [illegible]

[illegible]
[illegible] at CRC - but CRC [illegible]
long time studies of [illegible]
[illegible] would be needed. [illegible]
our neighbours [illegible]! - [illegible] meeting at 12/13.

2028541550

BRC/UKC Meeting - ? speakers

23rd European Insurance - CA meeting

18th [illegible] - Lamont [illegible] at [illegible] room
Paris room

Richard Binning meeting conversation with Roger Walk
Dusseldorf connection
financing

Meeting at [illegible] before [illegible] with Roger/Wally
broad objectives etc etc ... ? - What about Roger?
Ring [illegible] - 3 [illegible]

Richard Any further news from [illegible] - with Chris [illegible]
- [illegible] paper can I have a copy?

2028541551

Tuesday March 9th

ACJ press cutting 5840 – 5700

N.B: Knapp, D.L. et al. 1992:- "Fetal exposure to nicotine in passive maternal smoking as detected by meconium analysis."

Conclusion: "Quantitative measure of fetal exposure to tobacco smoke is possible by meconium analysis. Of significance, infants of passive smokers showed equivalent MCC as in those whose mothers smoked. Although no significant effects of smoking were observed in the infants measurements, a larger population is needed to study these effects."

~~Epilepsy:- 21 97~~
~~80 - 1187, 1207, 1213~~
~~192 55~~
~~201 223, 235~~
~~211 566~~

Richard: Sel Rev. 282+. 8794.

Re study ① Do correctly, do analysis correctly +CO group:-
②

Dates for meeting Wolfe etc at Wolfs.

wk 12. (Mon 22/Tues 23rd) = Lee & Jane.
– Thu. 25/Fri 26th –
wk 13 Mon 29/Tues 30th
Thu 1st/Fri 2nd.

} Call Wolf – re Rogrow

20285541552

Fundamentals of Risk assessment according to Ecology Law Quarterly. (Vol 19: 269).

E.P.A. concentrated on but not that important as rules are not rigid & not the same as other agencies.

= 4 steps:

Hazard identification; dose-response evaluation; exposure assessment and risk characterisation:-

'Good' risk characterisation contains not only a final risk number but also a discussion of the uncertainties and assumptions behind the assessment, but unfortunately this step is rarely taken.

Hazard Id

Epidemiology - not always possible; always 'too late'.

Animal tests - species extrap; M.T.D; low dose extrapolⁿ

Carcinogenic classification. A, B1, B2, C, D, E.

"CRAVE" Carc. Risk Assessmt. Verification Endeavour = reviews scientific evidence for these class.

Dose-response evaluation:- 1). carcinogens zero threshold ?ble.

2). Shape of dose response curve used to extrap from high to low doses.

E.P.A use linear to "err" on the side of caution.

For arguments on other models refs are given....

Exposure assessment:

Population based exposure and Max. exp. individual - MEI.

MEI may be highly elevated "unrepresentative".

Risk characterisation

Derived from Q1 of dose-response calcn & exposure assessment but should have 'qualification' added.

E.P.A state a Risk characterisation should contain

a) a discussion of the "weight of the evidence" for carc (e.g. classification)

b) A summary of the various sources of uncertainty

c) a report of the range of risk - (0 — Eff. estimate)

2028541553

Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

The Delaney clause:-

= zero risk statute:

1958, The Delaney clause prohibits any pesticide residues "if it is found ... to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives to induce cancer in man or animal"

From the beginning implementation of the Delaney clause was problematical.
∴ EPA was reluctant to identify cancer risks under the clause.
⇒ 1988 "Regulations of Pesticides in Food: Addressing the Delaney Paradox" published by E.P.A.
Now OPP do use hazard assessment and QRA - Delaney cause applied unless risk is negligeable

p304 Some statutes allow Risk-Benefit balancing: TSCA & FIFRA
e.g. Pesticides under FIFRA

---

e.g.s of how risk assessment and technological feasibility interact can be found through the Safe Drinking Water Act and the Clean Water Act.
SDWA ⇒ MCLG = Max. cont. level goals = safe. = guide, not enforceable
⇒ MCL = Max. contaminant levels = standard, enforceable.
MCL = as near to MCLG as technically feasible.
MCLG's for group A or B carcins = zero. } highly protective.
MCLG's for group C = benchmark.
MCL often at practical quantitative limit.
e.g. Benzene - State diffs in 'feasibility' e.g. California, Florida etc. Ben = 1 µg/L
whereas EPA = 5 µg/L.
CWA - No conc of cancer = safe - acceptable risk = 10^{-6}., States can choose between 10^{-5} & 10^{-7}
Many MOE assumptions/generalisations in assessment of then risk.
This is not calculated on a worst case basis.

Re hazardous waste = defined as hazardous when QRA > 10^{-5}
OSW, 1990 = acceptable incremental lifetime cancer risk to hypothetical MEI
① for A & B carcs = 10^{-6}; ② for C carc. = 10^{-5}. } ≡ Bizarre?

p369 - EPA Risk Assessment - summary = varied policies but in general risks greater than 10^{-4} regulated, less than 10^{-6} left. Because diff assumptions

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are frequently made - cannot 'compare' apparently similar risks.

p322. "However, they never prescribe how cancer risks are to be calculated and rarely specify what levels of cancer risk are unacceptable (with the possible exception of the .... Delaney clause)."

Summary. variations in E.P.A. QRA.

① What 'person' category - e.g. Max Exp. Individual
Population based risk etc etc....

② 'bright line' risk value

Looking to future recommendations -

p342. "As long as the degree of scientific uncertainty in cancer risk assessment is large, the choice of acceptable risk levels for use in regulatory decisions will be of secondary significance.

p360. "Our analysis suggests that the recent push for mandating numerical levels of acceptable risk in environmental legislation is misguided."

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Wednesday 10th March 1993.

1. See HGR re dates for InBifo.
2. Ring Wolf [Frank Guillotti - dates?]
3. Ring Ragnar Rylander.

S70

R&R. 25 32 07

Wolf:

Ragnar visiting - 22nd April.

Why? - [illegible] - 2 possible

Call [illegible] re precedents / policy for employing women / [illegible]

England [illegible] study on the effectiveness of prevention

[illegible] responsibility to report [illegible] results

Edmond [illegible]

Tony [illegible] [illegible]

[illegible]

[illegible] basis [illegible]

Ring [illegible] Chantal Cressole [= Next week!]

[illegible]

Ring [illegible] Thank [illegible]

Ring Richard re comments on Manuscript!

Chaumiers - surface a poire - glissance: 3 km - 10 D 17

Tennis: Emulle tennis poire.

50 Frs (L)

Ball / Racquet - (19h)

Mardi - 19h.

Commencer 19 (Mardi 20)

Friday 12th March

1. Ring Dezuanni - apologise to panel.
2. ~~Ring Tennis Marin~~ - to cancel 33 73 73
3. Ring 039 23 64 53 Roselyne Erard 6 lessons - Tues/Wed pm vers 7h? dès Apr. 20th?
4. Brussels meeting

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Clin. lab. Haemat. 1992, 14: 281-287. K. Kario; T. Matsuo & K. Nakao.

Cigarette smoking increases the mean platelet volume in elderly patients with risk factors for Atherosclerosis:-

142 elderly subjects, (58♂, 84♀ 77.1 ± 7.7 years)
Group I = healthy nonatherosclerotic nonsmokers (10♂ 32♀)
Group II = healthy smoking nonatherosclerotic men (23♂ 2♀)
Group III = nonsmoking atherosclerotic (12♂, 43♀)
Group IV = smoking atherosclerotic (13♂, 7♀)
No age diff between the four groups.
Claim that smoked have an increased platelet volume:-

	I	II	III	IV
MPV	7.9 ± 0.9	8.1 ± 0.7	8.3 ± 0.8	8.4 ± 0.7*

sig $P<0.05$

↑ in MPV have been described in various arterial diseases & may play an imp. role in the progression of atherogenesis and thrombosis.

Journal of Human Hypertension (1992) 6: 359-365. Hypertension follow-up group.
Effect of cigarette smoking on the J shaped relationship between treated blood pressure and cardiovascular disease.

1985-1988, 6,986 patients.
Occurrence of CVD monitored from 1986 to 1990.
2,654♂, 4,171♀
2,518 aged 50-59; 2867 aged 60-69; 1440 aged 70-75
Follow up gave 241 IR events, 52 patients died
J shaped curve with treated SBP in ♂, ♀ & all.
Smoking status known for 99% of total.
J shaped curve not present in non-smokers but was only in smokers.
No relationship found for DBP - only SBP.

~~ESC - Brussels meeting~~

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Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Monday March 6th.

Rabbit Atherosclerosis studies:

① Studies in rabbits with smoking (active or passive).
② Studies in other animals with smoking - cockerels, pigeons etc etc.
③ Overviews / reviews of literature in these areas:

①&②- Ask Rosemary to do a literature search on animal studies for atherosclerosis and smoking, (either sidestream or mainstream smoke) Animals would include Rabbit; cockerel; Cynomolgus Monkey; White carneau Pigeon amongst others, pig, turkey

③:- from Rosemary search on Atherosclerosis rabbits Reviews:- 18/02/93:-

Ref #21:-
Hadjiisky, P., Bourdillon, M.C., & Grosgogeat, Y.
"Experimental models of Atherosclerosis: contribution, limits and trends."
Arch. Mal. Coeur. Vaiss, 1991. Nov. Vol 84(11) p1595-605. In French!!

N.B. re rabbit says "The rabbit, also free of spontaneous atherosclerosis, is extremely sensitive to lipid-rich diets, but the lesions induced resemble more xanthomatosis than an atherosclerosis."
Conclusion appears to be that the pigeon would be the best 'model' - but this is more for studying mechanisms than causes I would say). -

(Abstract only original article is on order)

Ref #26:-
Kritchevsky, D. "Dietary fat and experimental Atherosclerosis"
Ann. J. Tissue Reactions 1991. Vol 13(2) p:51-62.
Reviews studies relating to the effects of fat unsaturation & fatty acid composition on the development of experimental atherosclerosis in rabbits. The results derived from the feeding of various fats or similar studies are fairly consistent on an atherogenic cholesterol-free semipurified diet. In general, the severity of atherosclerosis is inversely related to the level of fat saturation.

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Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000

Ref #39:-

Fuster, V, Ip, J.H., Badimon, L., et al.....

"Importance of experimental models to the development of clinical trials on thrombo atherosclerosis".

Circulation, 1991; 83(6 suppl). P. IV15 – 25)

"Based on experimental findings, we present and discuss a pathological classification of vascular injury or damage and its role in the pathogenesis of various vascular diseases."

"In summary, we are entering an exciting era in vascular research. Significant advances in our understanding of vascular injury or damage as well as the interaction of blood cells and lipids with the vascular wall have allowed us to formulate new experimental strategies with subsequent clinical application in the prevention and progression of these vascular diseases.".

Ref. #47:-

Watabayashi, K. (1990)

"International commission for protection against Environmental Mutagens and Carcinogens. ICPEMC working Paper 7/1/3. Animal studies suggesting involvement of mutagen/carcinogen exposure in atherosclerosis."

Mutat. Res. 1990, 239 (3), 181-7.

To elucidate causative agents of atherosclerosis – evidence of monoclonal origin of atherosclerotic plaque in women prompted the study of the involvement of mutagenic/carcinogenic in the development of atherosclerosis. Polycyclic hydrocarbons, including 7,12-DMBA and BaP were shown to act as initiators or accelerators of atherosclerotic plaque formation in chicken, pigeon, mouse, rabbit & rat.....

Of considerable interest in reality.

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N.B. Talking points from C&B:-

① Exposure chamber totally inadequate :. should reconsider my proposal to use the same chamber - there can be no, or little, justification on scientific grounds.

② What are these 'non respirable particles C&B refer to in point ③? Is this just the diff between total particulate and respirable particulate & if so may be due to measurement diffs? - Furthermore is it true that ETS is all respirable particulate?

—//—

N.B from literature search from Rosemary on Atherosclerosis and smoking in animals.... 15/3/93....

Ref #6:
Penney, D.G. & Hawley, J.W. (1991)
"Is there a connection between CO exposure and hypertension"
Environ. Health. perspect. 1991 Nov 95: p91-8.

states:-
"It has been asserted that chronic CO exposure increases the development of atherosclerotic disease; however, convincing evidence from animal experimentation is lacking. Nevertheless, CO may elevate plasma cholesterol and does appear to enhance atherosclerosis when serum cholesterol is greatly elevated by diet".

—//—

Following this - begs the following questions:-

① Do the levels of CO exposure reported by 2nd hand smoke correspond to those reported in the literature to have such an effect.

② Could even the very low levels of CO in real ETS have roughly similar effect? — i.e. could this evidence us anyway

③ How strong is the evidence for CO in rabbits - hypercholesterolaemic or otherwise.

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Source: https://www.industrydocuments.ucsf.edu/docs/tscl0000